REMARKS

Entry of this Amendment is proper under 37 C.F.R. § 1.116 because the Amendment places the application in condition for allowance for the reasons discussed herein; and does not raise any new issues requiring further search and/or consideration as the amendments amplify issues previously discussed throughout prosecution. Entry of the Amendment is thus respectfully requested.

Claims 21-39 and 41-43 are now pending. Claim 21 has been amended herein. Basis for this amendment may be found throughout the specification and claims as-filed, especially at claim 21 as-filed and page 6, lines 9-11, page 6, lines 20-22, page 7, lines 16-18 and page 8, lines 4-6, of the specification. Thus, no new matter is submitted by way of this amendment.

Applicants reserve the right to file a continuation or divisional application directed to any subject matter canceled by way of this Amendment.

REJECTIONS UNDER 35 U.S.C. § 102(b)

Claims 21-32 stand rejected under 35 U.S.C. 102(b) as purportedly anticipated by Southern *et al.* Applicants respectfully traverse.

For proving anticipation, "anticipation requires the presence in a single prior art disclosure of all elements of a claimed invention as arranged in the claims." *Jamesbury Corp. v. Litton Industrial Products, Inc.*, 225 U.S.P.Q. 253, 256 (Fed. Cir. 1985).

The currently pending claims are directed to a method of sequencing multiple different DNA templates in the same reaction zone simultaneously. Southern fails to disclose a method of simultaneously sequencing multiple DNA templates in a single reaction zone. In the interest of expediting prosecution, and to further clarify what is meant by the phrases "same reaction zone" and "plurality of single stranded DNAs", Applicants have amended independent claim 21 herein.

In response to the argument that Southern does not disclose a heterogeneous population of single stranded DNAs in the same reaction zone, the Examiner stated that this was not the case as a long chain of single stranded DNA can be considered as "several different small single stranded DNA (heterogeneous DNAs) joined together".

In response, Applicants submit that the skilled artisan would not interpret the phrase "a plurality of single stranded DNAs to be sequenced", as recited in currently pending claim 21, to refer to a single long chain of single stranded DNA. Instead, the skilled artisan would understand this phrase to refer to more than one separate molecule of single stranded DNA. This interpretation of the phrase "a plurality of single stranded DNAs to be sequenced" is supported by the language of the claim itself, which refers to "each DNA"

implying that the DNAs are separate entities. Applicants also refer to the instant specification, on page 3, lines 5-6, which describes the target DNA populations as consisting of DNA fragments. Page 6, lines 20-22, of the specification refers to the DNA fragments as molecules. Applicants thus respectfully submit that the skilled artisan, upon r would appreciate from the specification as a whole that the application provided a method for sequencing single stranded DNA molecules.

The Office Action states that Southern discloses the sequencing of multiple "templates" or DNA molecules. However, as disclosed in Southern, sequencing does not take place simultaneously. Instead, Southern discloses that the sequencing reactions are performed in parallel, each template being present in its own distinct reaction zone (*e.g.*, on a pin).

Therefore, the methods of the claimed invention and the methods Southern may be distinguished by the number of templates or DNA molecules present in a single reaction zone. Applicants submit that the fact that the claimed invention recites multiple templates in a single reaction zone renders the claims novel over the cited reference. By way of further explanation, Applicants provide the following comments regarding the phrase "reaction zone".

The Examiner appears to define "same reaction zone" as a common sequence on a plurality of DNA templates where hybridization reaction takes place. Instead, Applicants

submit that the skilled artisan, based on what is disclosed in the specification and known in the art, would give the words "reaction" and "zone" their common meaning. The instant specification does not provide any motivation for one skilled in the art to interpret "reaction zone" to mean anything other than a container or region where the templates are located in which the sequencing reaction takes place. In fact, the specification defines "reaction zone" as a region in which the tags are detected from an individual sequencing reaction and a region where sequencing occurs (see page 7, lines 16-18). The specification states "the invention provides a method for analysing heterogenous sub-populations of nucleic acids without spatially resolving them" [emphasis added]. The phrase "without spatially resolving them" indicates that the templates are present in the same container or region and are sequenced without the need for separation.

The parallel analysis of multiple templates or DNA molecules disclosed in Southern is distinct from the simultaneous analysis of multiple templates or DNA molecules in the same reaction zone (or without spatial separation). Specifically, if multiple templates or DNA molecules are analyzed simultaneously in one reaction zone or without spatial separation, there must be a method of analyzing the data generated so that particular data can be assigned to the particular template/DNA molecule that generated it. For this reason, the present invention requires that each DNA template/molecule is present in a unique amount. In any given sequencing cycle, the frequency of (or signal size from) each probe

will vary with the amount of the corresponding template/DNA molecule present in the reaction zone. However, Southern does not disclose that each template/DNA molecule must be present in a unique amount.

By way of further explanation of the differences between the sequencing method defined by claim 21 amended herein and the sequencing reaction disclosed in Southern, Applicants provide the following diagrams, submitted as Appendix A. These diagrams support Applicants arguments regarding the differences in the sequencing methods of Southern and the present application, and also in explaining why the method of Southern could not be used to sequence multiple templates in the same reaction zone.

The diagram entitled "Southern 1- The components" shows a single stranded template/DNA molecule, and a probe which is complementary to a region of the template/DNA molecule.

The second diagram, "Southern 2 - Hybridizing Template to a Probe Present in a Reaction Zone", provides two diagrams. The diagram on the left shows one template/DNA molecule hybridized to a probe in a reaction zone. The diagram on the right illustrates why the method of Southern does not permit the sequencing of two templates/DNA molecules in a single reaction zone. In this diagram, two distinct templates/DNA molecules have been hybridized to two probes present in the same reaction zone.

The third diagram, "Southern 3 - Ligating Mass Tagged Oligonucleotides", shows the next phase of the sequencing reaction in which mass tagged oligonucleotides have been hybridized to the templates/DNA molecules and been ligated. In the diagram on the right hand side, it can be seen that distinct mass labeled oligonucleotides have hybridized to the difference templates/DNA molecules present in the reaction zone, show the mass spectra generated following cleavage and detection of the mass tags. In the figure on the left-hand side, the single mass tag detected can be used to determine the sequence of the template/DNA molecule adjacent to the region complementary to the probe. In the figure on the right, two peaks are seen on the mass spectrum. It is not possible to determine which mass tag relates to which template and so no sequence information can be deduced.

The fifth diagram " Schmidt & Thompson 1 - The Components", illustrates the method of claim 21 of the present invention. The components of the sequencing method of claim 21 include two or more templates/DNA molecules present in different quantities and a probe that is complementary to a sequence present on all these templates/DNA molecules.

The sixth diagram, "Schmidt & Thompson 2 - Hybridizing Multiple Templates to Array", shows the templates/DNA molecules following hybridization to probes present in a single reaction zone.

The seventh diagram "Schmidt & Thompson 3 - Ligating Mass Tagged Oligonucleotides" shows the next phase of the sequencing reaction in which mass tagged

oligonucleotides have hybridized to the templates/DNA molecules and been ligated to the probes. The diagram illustrates that different mass labeled oligonucleotides have hybridized to the different templates/DNA molecules present in the reaction zone.

The eighth diagram, "Schmidt & Thompson 4 - Cleave and Detect Mass Tags" shows the mass spectrum generated following cleavage and detection of the mass tags. Two peaks are seen on the mass spectrum. However, the abundance of these peaks is different. The abundance of the tag is related to the quantity of the template/DNA molecule to which the corresponding mass tagged oligonucleotide was bound. Therefore, the sequence of each template/DNA molecule can be determined using the mass tags.

Thus, in light of the amendment to claim 21 and the arguments presented herein, Applicants submit that the present invention is novel over Southern. Applicants respectfully request that the rejection be withdrawn.

Claims 21-25 and 27-32 stand rejected under 35 U.S.C. §102(a) as purportedly anticipated by Macevicz *et al.* Applicants respectfully traverse, as the cited reference fails to disclose all of the elements of the claimed invention, as amended herein.

Macewicz discloses a method for analyzing a single nucleic acid template by dividing a population comprising multiple copies of that template into separate aliquots. In each aliquot, a different initializing oligonucleotide is added to the target template so that

each initializing oligonucleotide starts sequencing at a different point in the target sequence. Probe oligonucleotides are then ligated to the initializing oligonucleotide, identifying the base adjacent to the initializing oligonucleotide. Thus, in this way, several bases of the target sequence are identified.

Therefore, the method of Macevicz only discloses sequencing a single template or DNA molecule. Applicants further note that although Macewicz describes several reaction zones, only one template or DNA molecule is present in each of these reaction zones. Thus, claim 21 as amended herein, is novel over Macewicz.

Macevicz is silent as to the issue of sequencing multiple templates/DNA molecules in the same reaction zone. In addition, Macevicz does not disclose using multiple templates/DNA molecules that are present in different amounts.

Thus, in light of the amendment to claim 21 and the arguments presented herein, Applicants submit that the present invention is novel over Macewicz. Applicants respectfully request that the rejection be withdrawn.

Claim Rejections under 35 U.S.C. §103

Claims 21-39 and 41-43 stand rejected under 35 U.S.C. § 103(a) as purportedly unpatentable over Southern *et al.* in view of Stratagene Catalog. Southern *et al.* do not teach the motivation to combine all the reagents for identifying a base at a target position in

a single-stranded sample DNA sequence in the form of a kit. However, the Office Action states that it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to combine all the reagents into a kit format as discussed by Stratagene catalog. Applicants respectfully traverse.

In proceedings before the Patent and Trademark Office, the Examiner bears the burden of establishing a *prima facie* case of obviousness based upon the cited references. The Examiner can satisfy this burden by showing, first, that the cited prior art coupled with the general knowledge at the time of the invention must contain some suggestion or incentive to motivate a skilled artisan to modify or combine references. *See In re Fine,* 837 F.2d 1071, 1074, 5 U.S.P.Q.2d 1596, 1598 (Fed. Cir. 1988); *In re Skinner*, 2 U.S.P.Q.2d 1788, 1790 (Bd. Pat. App. & Int. 1986). Second, the Examiner must show that the modification or combination of prior art references must have a reasonable expectation of success (at the time of the invention). *See Amgen, Inc. v. Chugai Pharm. Co.*, 927 F.2d 1200, 1209, 18 U.S.P.Q.2d 1016, 1023 (Fed. Cir. 1991). Lastly, the Examiner must show that the cited or combined references teach each and every limitation of the claims. *See In re Zurko,* 111 F.3d 887, 888-89, 42 U.S.P.Q.2d 1476, 1478 (Fed. Cir. 1997); *In re Wilson,* 424 F.2d 1382, 1385, 165 U.S.P.Q. 494, 496 (C.C.P.A. 1970).

The cited reference, alone or in combination, do not provide suggestion or incentive to motivate a skilled artisan to modify the references or provide reasonable expectation of success. As discussed above, Southern (even in combination with the secondary reference) fails to recite each and every limitation of the claims.

The Office Action further states that the kit claims are obvious over the disclosures of Southern and the Stratagene catalog. Applicants submit that these references, in combination or alone, fail to provide motivation to provide a kit comprising a means for resolving a measured quantity of the hybridized probe into quantities which correspond to unique amounts of the templates to which the probe hybridizes. Applicants note that Southern, the primary reference, is silent as to the issue of sequencing multiple templates/DNA molecules in the same reaction zone. Thus Southern fails to provide any motivation to arrive at a sequencing method that permits sequencing of multiple templates/DNA molecules without spatial separation. Further, there is no expectation of success, because even if the skilled addressee had attempted to use the method of Southern to sequence multiple templates/DNA molecules in the same reaction zone or without spatial separation, the skilled artisan would have encountered the problems illustrated in Figure 4 (because the sequence information could not be related to specific templates/DNA molecules). Finally, as Southern does not disclose sequencing templates/DNA molecules present in different amounts, the skilled artisan would not have attempted to modify the

sequencing method of Southern to sequence templates/DNA molecules present in different quantities.

Thus, in light of the amendment to claim 21 and the arguments presented herein, Applicants respectfully request that the rejection be withdrawn.

CONCLUSION

Based on the foregoing, this application is believed to be in condition for allowance. A Notice to that effect is respectfully solicited. However, if any issues remain outstanding after consideration of this Amendment and Reply, the Examiner is respectfully requested to contact the undersigned so that prosecution may be expedited.

Respectfully submitted,

BURNS, DOANE, SWECKER & MATHIS, L.L.P.

Date: June 9, 2003

By: _____
Deborah H. Yellin
Registration No. 45,904

P.O. Box 1404
Alexandria, Virginia 22313-1404
(703) 836-6620